SIR RONALD ROSS AND THE EVOLUTION OF MALARIA RESEARCH*

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OF all the discoveries in the field of medicine which have graced this turbulent century, none have been more arduous or more dramatic than those concerned with malarial fevers, their nature, their mode of transmission, the life cycles of their causative pathogens, and their control. One may speak of this great scientific drama as a war of 100 years; battles won and lost, peaks conquered and abandoned. The campaign still goes on.

The heroes and the captains of these battles came from many lands and from different continents; their battle stations were far apart in time and in place: in Constantine, Algeria; in Secunderabad, India; in the Pontine marshes and on the wards of the Spirito Santo Hospital in Rome; in Kharkov, Russia; in Horton, England; in Cairns, Australia; in the Naval Medical Center at Bethesda, Md.; in the London School of Tropical Medicine; and in a forest gallery of Katanga in the Congo—discoveries linked together likes arches in a luminous bridge that spans a dark river.

Today we commemorate an event in the history of science that had a profound and lasting effect on global public health—a discovery which in its narrowest application illuminated the field of malariology and by its decisive demonstration of the sporogonic cycle of plasmodia in mosquitoes clearly indicated the road to control. In a wider sense this discovery served as a base for assaults upon other insect- and arthropod-borne diseases—the most formidable and destructive foes of mankind throughout the ages.

Today we evoke anew the memory of Sir Ronald Ross, the man behind this discovery, whose spirit and vision, above all, whose perseverance, brought about this victory. And from the pages of his writ-

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ings—the science and the poetry—and from the stations of his wandering years we may attempt to see the golden mosaic of his soul.

The malarial fevers have been with us for millenia. They accompanied man from the jungles and primeval forests to the primitive huts of mud and straw, and later to the walled cities on the banks of overgrown rivers. Almost all the ancient civilizations—those of the Mediterranean basin, the Near and Middle East, and the Far East—arose in delta regions of great rivers; all these were regions of vast swamps, mosquitoes, and swamp fever. It is no wonder that clinical observations and descriptions of these fevers are to be found in ancient Chinese and Sanskrit texts, in Greek and Latin medical manuscripts, in Hebrew and Arabic treatises, and in medieval and Renaissance writings. For the malarial fevers had a countenance all their own. They appeared suddenly, accompanied by severe chills; they released their grip abruptly, inducing profuse sweat and relief. They produced a triad of signs—intermittent recurring fever, anemia, and enlargement of the spleen. Their seasonal onset was observed and described: *la terzana benigna primaverile*, the benign tertian spring fever; *la febbre perniciosa estivo-autunnale*, the pernicious fever of late summer and autumn. These fevers struck the young and the old, the poor and the rich. Their association with stagnant waters was recognized of old; and legends of heroes who drained pestilential swamps and redeemed the land abound in ancient epics and other poems. Armies that crossed those fertile valleys and camped by those waters suffered heavily from the fevers.

Whence came these fevers? How were they carried? These questions remained unanswered even after Louis Pasteur and Robert Koch had demonstrated the bacterial origin of many diseases.

The first assault on these problems was undertaken by Thomas Sydenham and by Francesco Torti after the introduction of cinchona bark as a specific treatment for malaria. Francesco Torti[1] (1712), through acute clinical observation was able to separate fevers into those susceptible to cinchona and those resistant to it. This was the first use of a drug in the differential diagnosis of disease. In the middle of the 19th century H. Meckel recognized the malarial pigment in the spleen and the liver, and its association with the swamp fevers became known.

The arrival of the Pasteurian era did not bring clarification; rather, it added confusion. A microorganism, *Bacillus Tomassi-crudeli*, isolated from the Pontine marshes near Rome, was implicated as the causative

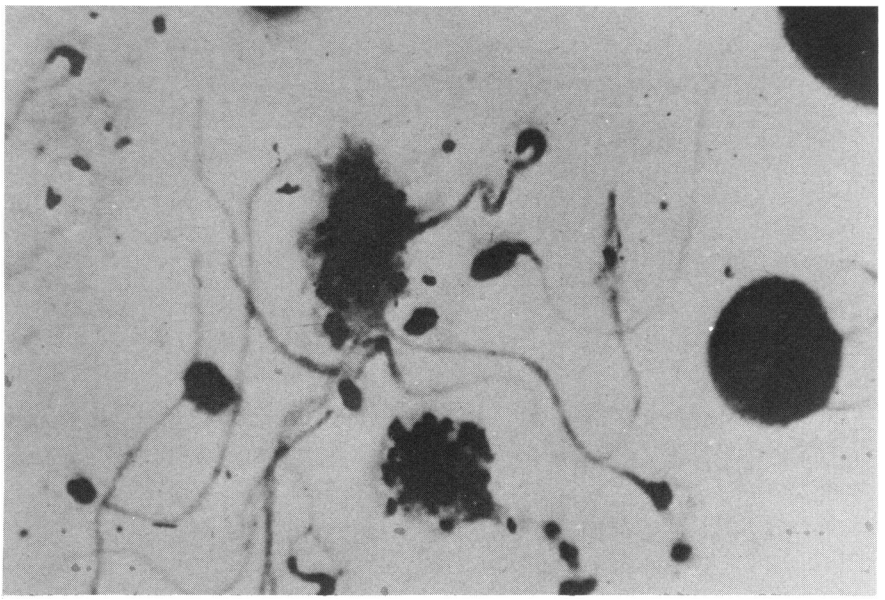

Fig. 1. Exflagellation of a microgametocyte of *Plasmodium falciparum.*

agent of malaria. Allegedly the ailment was spread by the inhalation of pestilential nocturnal air emanating from the miasmic marshes. The bacillus soon found many believers.

On November 6, 1880, Alphonse Laveran,[2] while studying the blood of malarial patients, observed the most dramatic event in the life of a plasmodium—exflagellation of the microgametocyte (Figure 1). In the lashing movements of the flagella and in their precursors, the hyaline pigmented bodies, he recognized the true parasitic nature of the infection.

His published observations were not accepted immediately. Many saw in the phenomenon a degenerative process: *l'agonie du mort d'un parasite.* It is to W. G. MacCallum[3] and E. L. Opie[4] (1897) of the Johns Hopkins University in Baltimore that credit must go for recognizing the true nature of this phenomenon as the fertilization of gametes and the formation of zygotes.

We should not deride the erroneous notions of the past, for we must recognize the great difficulties which our predecessors faced. Examination of blood was done by direct observation. Staining of the blood was yet to be developed and the oil-immersion lens was in its infancy. Many

Fig. 2. Sir Ronald Ross. Reproduced by permission of the Ross Institute, London.

an outstanding pathologist completely ignored those pale vacuoles in the red cells, sprinkled with granules of pigment. One must admire the genius of Camillo Golgi,[5] who under those conditions was able to differentiate the species of human plasmodia and to demonstrate the synchronicity of their intraerythrocytic growth with the clinical symptoms and the fever patterns. It was indeed the first demonstration of a biological clock so often described nowadays in nature.

Fifteen years had passed since Laveran's discovery, yet the mode of transmission of malaria still remained unknown. There were of course

visions, theories, and hypotheses. Giovanni Maria Lancisi[6] long ago, and A. F. A. King more recently (1883), pointed to insects as the possible vectors, and both Laveran and Manson suggested that mosquitoes might carry the fevers. But how? And by what mechanism?

In these twilight hours of the 19th century, destiny moved to introduce a new hero, a most unusual hero, Surgeon Major Ronald Ross (Figure 2), who was born on May 13, 1857, in India, the son of Sir C. C. G. Ross, a general on active duty.[7] The Ross family tree was old, the lineage Scottish and distinguished. For generations it had produced fighting officers and administrators for Her Majesty's Service on the turbulent frontiers of the empire. Ronald Ross' childhood and youth were spent in military encampments and in hill stations close to, yet far remote from the multimillion masses of the Indian subcontinent. Within the Spartan, authoritative nature which Ronald Ross inherited from his father there flowed a gentler stream—a passion for poetry, for music, and for art. This came to him from his talented and gentle mother. In 1875 he went to England and entered St. Bartholomew's Hospital for his medical studies. As a student of medicine he was a failure, for his poetic, restless nature winged in many directions: to pure mathematics, to literature, to poetry, and to music. He looked for noble aims, for a supreme act of chivalry in an age of dying knighthood.

In 1881 he entered the Indian Medical Service, determined to solve the problem of the malarial fevers. Malaria was the unknown perilous sea upon which he chose to sail. He commenced his studies in 1892, ill-prepared, knowing nothing of entomology, and little of blood and parasites. What he lacked in formal instruction he made up by voracious reading, by teaching himself and, above all, by stamina and perseverance. His life in the military service was bound by stifling regulations, boredom, and exhausting regimental marches from station to station. We find the echo of those hard years in his cycle of poems: *In Exile.*

In 1894, while on leave in England, Ross met Patrick Manson, who urged him to proceed with an experimental investigation of the role of mosquitoes in the propagation of malaria. Manson, who had demonstrated that Culex is the vector of Bancroftian filariasis, believed that mosquitoes took up the flagella from malarious blood and then died upon the waters and contaminated them. According to this hypothesis man infected himself by drinking contaminated water, the process being

Fig. 3. Sir Ronald Ross and Lady Ross outside the hospital in Calcutta, India, 1898. Reproduced by permission of the Ross Institute, London.

similar to the transmission of the guinea worm as suggested by A. P. Fedchenko (1870).

To this task Ross devoted all his energy and all the time he could spare from his regimental medical duties. For two and a half years he worked feeding mosquitoes on fever patients, dissecting the mosquitoes, and searching for the flagella (Figure 3). Alone, with nobody to counsel him, with few books to guide him, he mastered the dissection of mosquitoes and the identification of their organs and tissues—a vast ocean of cells and debris. Despite obstruction by superiors, despite illness and red tape, he carried out his investigations ceaselessly, reporting to Manson his results and the details of his failures.

The summer of 1897 was heavy and oppressive. The early monsoons did not cleanse the air. Ross was now 40 years old and had spent 16 years in the service. He was married and was the father of two children. His toil seemed unavailing. He felt he was near the end of his endurance and he contemplated leaving the service.

August 20 was an overcast and burning-hot day. Ross would remember it all his life. A haze hung over the plain of Secunderabad. The air was still and suffocating. In the early morning hours he visited his patients, devoting the rest of the day to dissection of mosquitoes which he had fed on Hussein Khan, a gametocyte carrier, four days earlier. Nothing new, the same old cells, the same debris, and no flagella. There remained three "dapple-winged" mosquitoes, of a new and different kind. Taking one of them, he carefully dissected it, systematically scanning tissues and cells. At last he focused on the stomach of the mosquito. Amid the epithelial cells of the midgut he saw a number of perfectly circular hyaline bodies, 12 microns in diameter. Each contained a few fine granules of black pigment, which he immediately recognized as identical with those he had found in the plasmodial crescents in the blood. Sealing the preparation, he made notes and drawings of the circular, pigmented spheres. Then he wrote a letter to Manson. On the next day, August 21, he dissected the last two dappled-winged mosquitoes; again he found spherical, pigmented bodies. This time they were larger than they had been the day before.

Two facts emerged and two deductions stood out clearly: 1) the spherical bodies were zygotes, and they grew; the parasite had a true developmental cycle in the mosquito vector. 2) the parasite of human malaria grew in certain mosquitoes only.[8]

Ross's journey was almost over: another few observations were needed, he thought, another experiment or two. He intended to keep the infected mosquitoes alive for longer periods and to follow the growth of the spherical bodies to their ultimate fate. But a sudden transfer to another military station interrupted his work, and months passed until Manson persuaded the Indian Government to assign Ross to special research on malaria in Calcutta (Figure 3). But now no human malaria cases were available to him and he turned to avian malaria. Within a few months, with the key to the problem in his hand, he was able to finish his studies. He had demonstrated the whole sporogonic cycle—the maturation of the oocysts, the penetration of the sporozoites into

the salivary glands, and their subsequent inoculation into the host by the bite of the infected mosquito. At last he had triumphed, and he postulated exactly the same cycle for the human malarial parasites. Avian malaria (followed by primate and rodent malaria in later years) proved to be a most important tool for solving some of the intricate problems of human malaria.

The Swedish Academy attested to the great impact of his pioneer work in awarding to Ross the Nobel Prize for medicine. But Ross's discovery was not an isolated event carried out in a void. The ripening of scientific ideas often occurs simultaneously in many lands, as apples fall from trees in different orchards far apart, tossed by the same mysterious breeze. In Italy, where malaria was endemic on a large scale, a group of brilliant scholars independently assaulted the age-old problem. Among them were distinguished clinicians and pathologists who had previously made notable contributions to many other fields in medicine: Ettore Marchiafava, Angelo Celli, A. Bignami, G. Bastianelli, F. Dionisi, and the redoubtable Giovanni Battista Grassi. They studied the pathology of the pernicious fevers and the relation between malaria and the prevalence of different mosquito species. The outcome of these studies was a momentous breakthrough, a clear and precise understanding of the specific relation between anophelism and malaria, and the elucidation of the complex life cycle of the human plasmodia. Their work followed Ross' discovery by a few months and, one may truly say, independently.

Rivalry may stimulate and enhance scientific work. It can also darken human relations, bringing anger and bitterness, which may linger long after the splendid wave has passed. For Ronald Ross, his discovery was the child of his innermost dreams; the hope and the vision which he had cherished and kept alive in the desert years. He could not let anyone snatch it away from him. This great and noble man could not acquiesce at the sight of others sailing the ocean which he had crossed alone. Accusations and rancor, letters, and statements on priority—even vilification—marred this splendid chapter of scientific discovery. For Ronald Ross, the injury was made even more bitter when he saw Grassi's splendid volume, *Studi di un Zoologo sulla Malaria*,[9] dedicated to his friend and mentor, Patrick Manson. The laurels and the honors he received, the voyages he made, the malaria control programs which he inaugurated, and the science of pathometry (mathematical epidemiology) which he created, did not assuage his injured pride or quiet the

vehemence of his soul. The storm has long subsided and the names of Battista Grassi and Ronald Ross stand beside that of Alphonse Laveran, three luminous arches of a noble bridge.

Within a few years after these classical discoveries, research on malaria gained greatly. In St. Petersburg, Russia, D. L. Romanowski[10] discovered the method of selective staining for malaria parasites and blood. This facilitated diagnosis and research and added fundamentals to the new discipline of hematology. Other scientific observations emanating from different countries added important details to our knowledge. The life cycle of the plasmodia was the leitmotiv of most of these studies, the central axis around which most of the research revolved.

The conception that developed in the beginning of this century and was still dominant in the 1930s was clear and persuasive. It was a complex system that included intraerythrocytic schizogony and gametogony in the blood, and sporogony in the mosquito vector. This conception derived additional strength from a paper published in 1902 by the great German biologist, Fritz Schaudinn,[11] discoverer of the *Treponema pallidum*. Schaudinn reported *in vitro* studies in which he claimed to have observed the direct penetration of sporozoites of *Plasmodium vivax* into the red-blood cells and their direct transformation into trophozoites. His scientific authority was so great that his work remained unchallenged until World War I. The events on the Macedonian front, 1916-1917, where the armies of France and Great Britain faced the German and Turkish armies in an area of high endemicity situated along the Vardar and Strymon rivers, disclosed the first crack in Schaudinn's assertions. Within a period of 18 months the British were forced to evacuate 110,000 victims of malaria. The French could not send a single fighting patrol into the line. This happened despite the administration of quinine, an "assured" curative and phophylactic drug. There was something wrong somewere! Why did quinine not protect if it acted on the blood forms, and sporozoites penetrated erythrocytes directly?

Following Wagner von Jauregg's[12] observations on the effect of malaria on neurosyphilis, centers for treatment of malaria were established at several places—Rome, Bucharest, Horton, England, and Tallahassee, Fla. These served as focal points for experimental research on malaria, and important results issued from them. Soon it was observed that when blood containing trophozoites was inoculated, it was possible to prolong or shorten the incubation period by varying the concentra-

tion of the infected cells. However the bite of a single infected mosquito or of 200 to 300 mosquitoes would not alter the latent period. There must be a hidden early cycle of the plasmodia somewhere! But where? Albert Einstein once said, "Nature hides its secrets through her intrinsic grandeur but not through deceit."

By the work of G. Raffaele, S. P. James, P. Tate, Clay G. Huff, and others, the tissue stages of avian malaria parasites were discovered. The primary stages of their growth were found in cells of the reticuloendothelial system, in macrophages, and rarely in primitive cells of the hematopoetic system. It appeared certain that a similar cycle would be found for the human plasmodia in similar organs and cells. A frantic search began. It ended in failure. World War II interrupted the search for the elusive stages and for their hiding places in the human body.

The huge casualties from malaria suffered by the allies in Sicily, North Africa, and the Near and Far East increased the urgency of the investigation. Exact knowledge of the sites and organs in which the sporozoites developed in man was not merely academic. The whole direction of research on the chemotherapy and chemoprophylaxis of malaria depended upon it.

In 1948 Shortt and Garnham[13] broke the mysterious code. They demonstrated that all human and simian plasmodia have a primary tissue stage in parenchymal cells of the liver—not in phagocytic cells, as had been assumed. They showed further that the incubation periods of the four different human plasmodia depend directly on the length of this tissue schizogony, which occurs before the blood is invaded. These dramatic experiments required the use of millions of sporozoites from thousands of infected mosquitoes, first in trials on *Plasmodium cynomolgi* in monkeys, later in human volunteers. The investigation revealed a schizogony that was totally unexpected but fitted beautifully and clearly into the complex pattern of the hemosporidian life cycle.

The new conception of a more complex cycle, based on four different phases in the life of a malaria parasite, required new and more accessible biological tools for experimentation. The introduction of rodent plasmodia, *Plasmodium berghei*,[14] in 1948 and *Plasmodium vickei*[15] in 1952, each with its specific morphology and cellular tropism, suitable for a wide range of small laboratory animals, brought a new dimension to experimental malariology. In their exoerythrocytic development in the parenchymal cells of the liver,[16] these plasmodia showed growth

patterns typical of mammalian malaria parasites. In clinical course, pathology, and immune reactions, rodent plasmodia in mice, albino rats, and hamsters mirrored all the known and unknown struggles of the malarial fevers of man. They were devoid of danger and they awaited man's deeply probing mind.[17] Within the past quarter-century rodent malaria has been part of a great contribution which has broadened our horizons by permitting large-scale experimentation in chemotherapy, in the effect of genetic strains of the host, and on immunity and host-parasite relations. This work has been done on a vast scale in many laboratories throughout the world. The vast onslaught is comparable to the mass climbing of a peak previously considered inaccessible. The recent successful transmission of *P. vivax*, *P. falciparum*, and *P. malariae Aotus* to the squirrel and owl monkeys[18, 19] further facilitated research on the clinical, biochemical, therapeutic, and immunological aspects of malaria. With this adaptation, human plasmodia lost their exclusiveness, the dark crown which they had so long held. Malaria, also, has been shown to be a true zoonosis occurring under special sylvatic conditions; this affirms the close and ancient link that exists between primate and human plasmodia, which have issued from a common archaic stem.

In the preceding paragraphs I have discussed the life cycles of the plasmodia. But since Ronald Ross' discovery malaria research has moved in many other directions. Investigative work has been done on applied mosquito control and bonification, entomology, chemotherapy, host-parasite relations, and immunological aspects, as well as on the effect of malaria on the course of concomitant infections such as schistosomiasis and Burkitt's lymphoma, and on malaria as a factor in the genetic selection of large African populations. The worldwide control measures encouraged, planned, and directed by the World Health Organization (WHO) Malarial Eradication Program have achieved spectacular results and great success in many countries, less success in others. Much of the globe still remains in the grip of endemic malaria. Mosquito larvae breathe; and mosquito control began with the application of oil to breeding areas. Control switched to Paris green, based on the selective killing of anopheline larvae through their ingestion of the poison by mouth. Modern residual-insecticide programs were based on a newer fact, the neurotoxic effect of DDT. But all these control programs need to rely on dedicated teams, on stamina, on an élan vital of the field

squads, and on true reporting of results. Such programs succeeded where the sense of responsibility, the aim, and the dignity of work accompanied the scientific application of knowledge. They failed when available scientific knowledge failed to provide guidance: e.g., with respect to outdoor-biting species of *Anopheles*. The problem was larger when newly emerged nations and societies proved unable to sustain a prolonged will and a lasting sense of dedication in the field and in the supervising teams. But this is only one aspect.

The sustained pressure of massive insecticide-spraying programs based on the hope of quick eradication has produced a powerful backlash, as some mosquitoes showed resistance to DDT. This phenomenon, like the drug-resistance of plasmodia, perplexes, shocks, and exasperates us, and only later brings us the realization that in nature nothing readily gives up a territory held. Nothing is ready to die, not even a microorganism or an insect.

Entomological research has revealed the intricate nature of species and races of mosquitoes and of biological complexes like those of *A. maculipennis* and *A. gambiae*. We have learned of zoophilic and anthropophilic races, of indoor biters and outdoor biters. New methods are planned and postulated: biological, hormonal, or genetic. They may succeed in the laboratory or in small pilot experiments in the field. They must be carefully judged as grand strategies. Long ago Nicholaas H. Swellengrebel, a wise and experienced naturalist, pointed out that in malaria there is no single master key for all the doors; there are many keys, each opening a single door to a single regional problem.

Research in chemotherapy has given us new and powerful drugs and with them a renewed sense of caution in their use. The discovery of some of them was based on scientific concepts and on fundamental observations of enzymatic and biochemical pathways or of the respiration of parasites. But our knowledge in this field is still very limited. Too much effort is devoted to the blind screening of thousands of compounds in the hope of isolating one powerful drug. Too little encouragement is given to the pursuit of fundamental knowledge.

For many years a kind of preimmunity, apparently unique or unusual, was ascribed to plasmodial infections. This limited concept has now moved toward the wider area of general immunology, since the host-parasite relations encountered in malaria and the phenomenon of resistance to malarial infection are now known to display patterns that

have been observed in other infections. To the outstanding work of Edmond Sergent, Christophers, Taliaferro, and Ciuca, new modern contributions have been added in recent years. From the studies of cellular and humoral immunity many a fascinating chapter has emerged. We have learned, for example, that immune reactions do not always represent protective phenomena. It has become clear that the different stages in the life cycle of the malaria parasite produce different antibody responses and that the intraerythrocytic stages cannot be used in active immunization against sporozoite-induced infections. New light has recently been shed on the antigenicity of sporozoites and on the possibility of inducing active protective immunity on a limited scale by inoculation with irradated sporozoites. A fascinating and complex image was apparent in other studies, in which antigenic variations of plasmodia were demonstrated to appear with each attack or relapse; this thus may explain in part the mystery of relapses.

New and more exact diagnostic methods for elucidating inapparent infections have been devloped. These should be used more frequently in epidemiological studies and in daily clinical investigations in order to prevent transfusion malaria.

Since the days of Ronald Ross the aim of malariologists has been the healing of the land—*la bonifica*. It is an old and Faustian dream—a dream of green and peaceful fields, of children playing in meadows clear of pestilential swamps. No single, all-powerful drug can achieve this goal, but the combined knowledge and efforts of science and the dedication of men on this shrinking globe can and must bring about the realization of this dream. The plasmodia which malariologists have used as tools will not be idle in the future. They are used today and will be used even more in future medical research in the perplexing puzzle of the anemias, in the study of neoplasms (for a plasmodium invading all cells, running amok, is acting like a neoplastic cell), and as active biological tracers. Research in malaria has already transcended malariology and has invaded new domains.

I think of Sir Ronald Ross and of his work and of his dreaming soul. I wish to remember him not as he appears to us in his old age, crowned with many laurels, lonely and forbidding, and easy to anger. But I remember him as he was in those arduous days in Secunderabad, when his poet's soul mingled with his towering intellect—Ronald Ross, the visionary, the believer, the man of steadfast heart; the man

who watched an evening sky on an Indian plain, saw a star, and wrote:

Far across the Loneland, far across the Sea,
Far across the Sands, O silver shining
Sister of Silence, Sister of the Dew,
Sister of the Twilight, lighten me.

Even art thou beaming; I, with eyes upcast,
Gazing worn and weary from this Dark World,
Ask of thee thy Wisdom, steadfast Eye of God,
That I be as Thou art while I last.

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